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Chronic Eosinophilic Pneumonia Associated With Cutaneous T-Cell Lymphoma

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Cutaneous T-cell lymphomas (CTCL) are diseases characterized by cutaneous infiltrates of malignant clonally expanded T cells. CTCL cells exhibit a cytokine profile consistent with T helper-2 type (TH_2) cells. Eosinophilic pneumonias are individual syndromes characterized by eosinophilic pulmonary infiltrates and commonly peripheral blood eosinophilia. CTCL and chronic eosinophilic pneumonia are rare clinical entities. We report a patient with the association of CTCL and chronic eosinophilic pneumonia. To understand the mechanism leading to the eosinophilia, we examined the patient's cytokine profile. This was consistent with a high TH_2 activity. Her interleukin (IL) 5, 6, and 10 levels were extremely high, while her IL-2 and interferon-γ (IFN-γ) levels (TH_1 profile) were low. We believe that eosinophilic pneumonia in this patient is probably secondary to high TH_2 cytokine levels induced by tumor cells. We suggest that eosinophilic pneumonia should be considered as a possible diagnosis in patients with CTCL who have respiratory complaints. Am. J. Hematol. 60:143–147, 1999.

Key words: cutaneous T-cell lymphoma; chronic eosinophilic pneumonia; T helper-2 type cells; cytokine

INTRODUCTION

Cutaneous T-cell lymphomas (CTCL) are diseases characterized by cutaneous infiltrates of malignant clonally expanded T cells [1]. CTCL cells exhibit a cytokine profile consistent with T helper-2 type (TH_2) cells [1]. Eosinophilia described in these patients represents a poor prognosis [2]. Eosinophilia is probably secondary to TH_2 cells' cytokine production of Interleukins (IL) 4–6 and 10 [1,3,4,5]. During the TH_1 response, TH_1 lymphocytes, through their overproduction of IL-2 and interferon-γ (IFN-γ), induce T-cell and monocyte activation, i.e., promote cell-mediated immune responses. TH_2 responses are associated with IL-4, IL-5, IL-6, and IL-10 overproduction which induce B-cell maturation, antibody-dependent immune activities, and a generally allergic immune response [6].

Although mild eosinophilia has been reported in CTCL [2], the association with eosinophilic pneumonia has not been so far reported. We report a case of a female patient with the association of the tumor stage CTCL and chronic eosinophilic pneumonia.

CASE REPORT

A 55-year-old female was hospitalized with respiratory failure. She was diagnosed as having CTCL four years earlier.

One and a half years before the current admission, an eosinophil count of $2{,}500 \times 10^6$ cells per liter was noted. Three months before admission, she complained of

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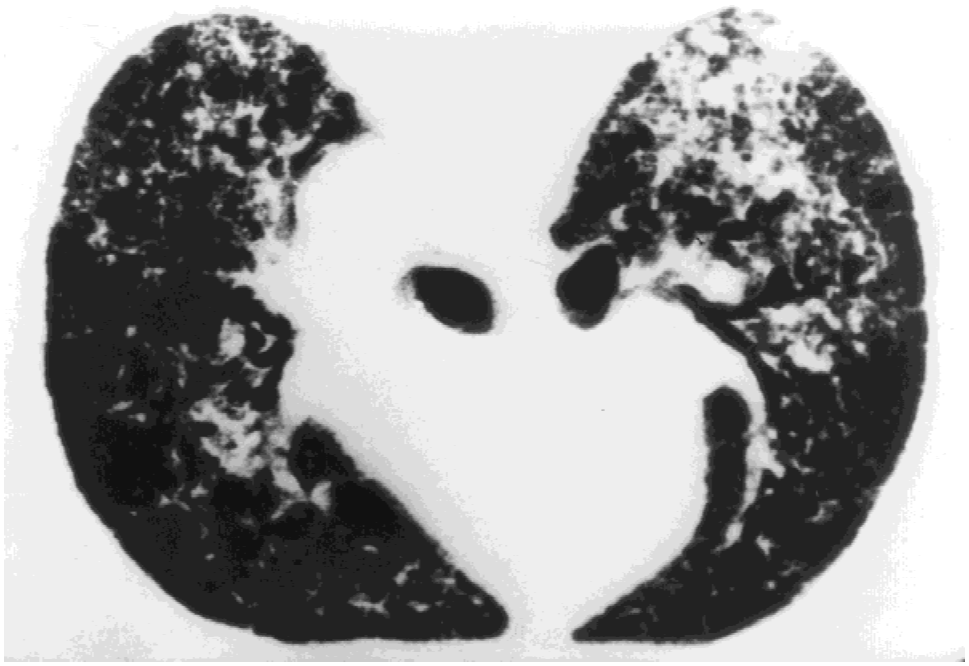

Fig. 1. CT scan of the chest showing diffuse intraalveolar and interstitial infiltrates.

cough and dyspnea. A chest X-ray and chest computed tomography (CT) scan (Fig. 1) demonstrated peripheral infiltrates. The patient underwent a bronchoscopy with transbronchial biopsy, which revealed an organizing pneumonia with an interstitial inflammatory infiltrate composed of lymphocytes, plasma cells, and a large number of eosinophils. The pathological findings were consistent with eosinophilic pneumonia. The patient was treated with prednisone, which was discontinued a week prior to the present admission.

On physical examination, the patient was tachypneic. Breath sounds over both lung fields were reduced with diffuse rales. The rest of the physical examination was unremarkable. Blood chemical findings were normal apart from an elevated lactate dehydrogenase and hypoxemia (arterial blood O_2 tension was 6.2 kPa). Total immunoglobulin (Ig)E was 847 units/ml (normal < 100 units/ml) and the eosinophil count was $5{,}800 \times 10^6$ cells per liter (38% of total WBC count). There was no hypergammaglobulinemia. A chest X-ray revealed diffuse bilateral alveolar infiltrates. She underwent a bronchoscopy with transbronchial biopsy, which revealed eosinophilic pneumonia (Fig. 2). A skin biopsy was performed and the histopathological studies did not demonstrate residual CTCL. High-dose steroid treatment was started with improvement in symptoms. She had a gradual improvement and was discharged with no dyspnea, PO_2 of 11.9 kPa on room air, and near-normal chest X-ray findings.

Six months later, a clinical relapse of the CTCL appeared, accompanied by eosinophilic pneumonia and peripheral eosinophilia ($5{,}500 \times 10^6$ cells/l). Following a course of high-dose steroids, cyclophosphamide and vincristine, the patient gained remission and both the pneumonia and the eosinophilia subsided.

METHODS

Serum levels of cytokines (IL-5, IL-6, IL-10, IFN-γ, and IL-2) and its receptor (sIL-2R) were measured by a solid phase ELISA (Quantikine HS R&D System, Minneapolis, MN). IL-6 was evaluated also by an AMI RIA kit (Advanced Magnetics, Cambridge, MA).

Southern blot analysis: Genomic DNA was prepared from skin biopsies using phenol-chloroform extraction following proteinase K treatment. *Eco*RI- and *Hind*III-digested DNAs (10 μg) were electrophoresed in 0.7% agarose gels and vacuum transferred to nylon membranes. The filters were hybridized with radiolabeled p^{32} β-T-cell receptor (TCR) probe, washed in buffers, and then exposed to X-ray films at −70°C [7].

RESULTS

Serum Cytokine Levels

We examined the possible association between the CTCL and the eosinophilic pneumonia. One such possibility could have been the exacerbation of the eosinophilia and hence of the eosinophilic pneumonia by cytokines excreted from or induced by the tumor cells. Table I shows cytokine levels before and during the eosinophilic pneumonia and after steroid treatment. TH_1 cytokines such as IL-2 and INF-γ were low throughout the course of her disease. TH_2 cytokines, including IL-5, IL-6, and

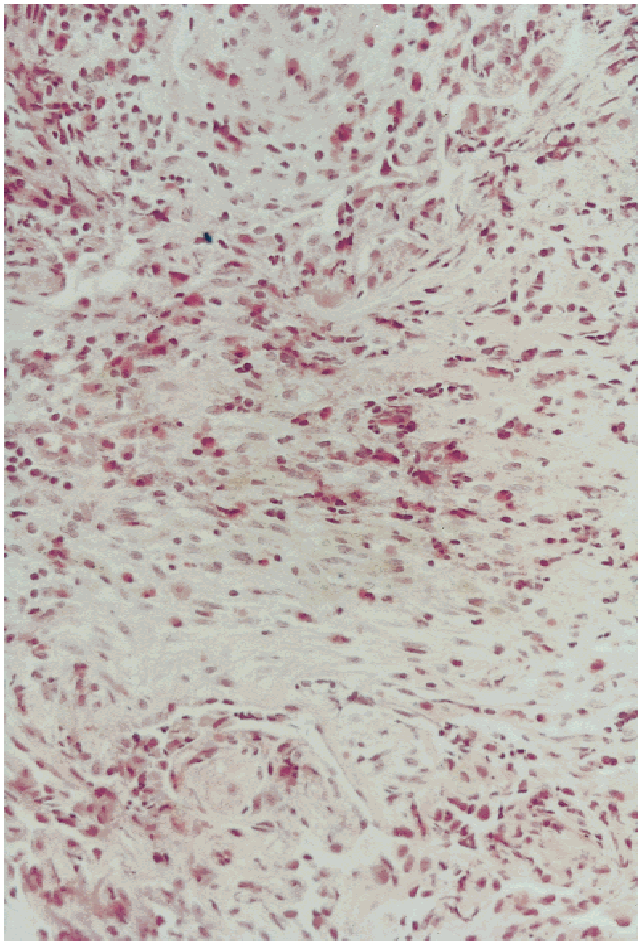

Fig. 2. Eosinophilic pneumonia with a prominent bronchiolitis obliterans component (center). The adjacent lung tissue shows interstitial and alveolar lymphohistocytic infiltrates. Numerous eosinophils are seen throughout the section. H&E, ×350.

IL-10 were high on admission and decreased 3–4 weeks following treatment with steroids.

Molecular Residual Disease of the CTCL

The patient was in a clinical remission from her CTCL when she developed the eosinophilic pneumonia. To learn whether there was an association between the CTCL and the development of eosinophilic pneumonia, a skin biopsy was performed and the TCR rearrangement pattern was studied. As shown in Figure 3, the TCR rearrangement pattern is identical to the one found in her tumor cells and different from the one obtained from her peripheral T lymphocytes. This indicates that despite clinical remission, the patient had a residual disease as displayed by molecular analysis.

DISCUSSION

CTCL are diseases characterized by cutaneous infiltrates of malignant clonally expanded T cells admixed with an inflammatory infiltrate [1,2]. Eosinophilic pneumonias are individual syndromes characterized by eosinophilic pulmonary infiltrates and commonly peripheral blood eosinophilia [9–13].

TABLE I. Serum Cytokine Levels

	Cytokine	Admission	Following 2 weeks of steroid treatment	Following 4 weeks of steroid treatment
TH_1 cells	Interleukin-2 (mean 13.7 pg/ml)	<14	<14	
	Interferon-γ (mean 0.7 pg/ml)	0	0.4	
TH_2 cells	Interleukin-5 (mean 1.4 pg/ml)	9	21	5.2
	Interleukin-6 (mean 1.6 pg/ml)	23	17	15
	Interleukin-10 (mean 2.8 pg/ml)	58	130	8.3
Other	β_2-Microglobulin μ/ml	1,184	851	1,643
	sIL-2R[a] (mean 483 μ/ml)	4,420	2,217	2,135

[a]sIL-2R, soluble IL-2 receptors.

CTCL and chronic eosinophilic pneumonias are rare clinical entities. Our patient had both. Previous reports have shown an association between lymphoid malignancies and eosinophilia including pulmonary eosinophilia [10–18]. Eosinophilia has been described in patients with CTCL [2–4,20]. In a study of 152 patients with CTCL, of 93 patients with specific enumeration of the eosinophil count, 21 had eosinophil counts greater than 700×10^6 cells/l. These patients had a poor prognosis compared with patients without eosinophilia [2]. The possible association of both syndromes in our case is probably related to the unique T-cell profile in CTCL.

CTCL cells may exhibit a cytokine profile consistent with TH_2 type cell [1]. These cells produce IL-4, -5, -6, and -10 and are inhibited by INF-γ originating from TH_1 cells [1,20]. This finding is consistent with the increase prevalence of hypergammaglobulinemia and eosinophilia in CTCL [1,2]. Stimulated TH_2 cells inhibit TH_1 cells by IL-10 production and induce eosinophilia by overproduction of IL-5 [5,6]. TH_1 cells are involved in directing the cytotoxic cell responses. Therefore, in some cases, CTCL may facilitate its own progression by inhibiting TH_1 cells, thus dismantling the immune system [1,5]. This inhibition probably does not occur in all CTCL cases. The higher mortality reported in patients with eosinophilia [2] may be due to higher tumor burden in these patients. The high level of TH_2 lymphocytes in these patients inhibits the TH_1 responses. Eosinophilia is a by-product of this situation.

We describe a patient with the rare combination of eosinophilic pneumonia and CTCL. To understand the

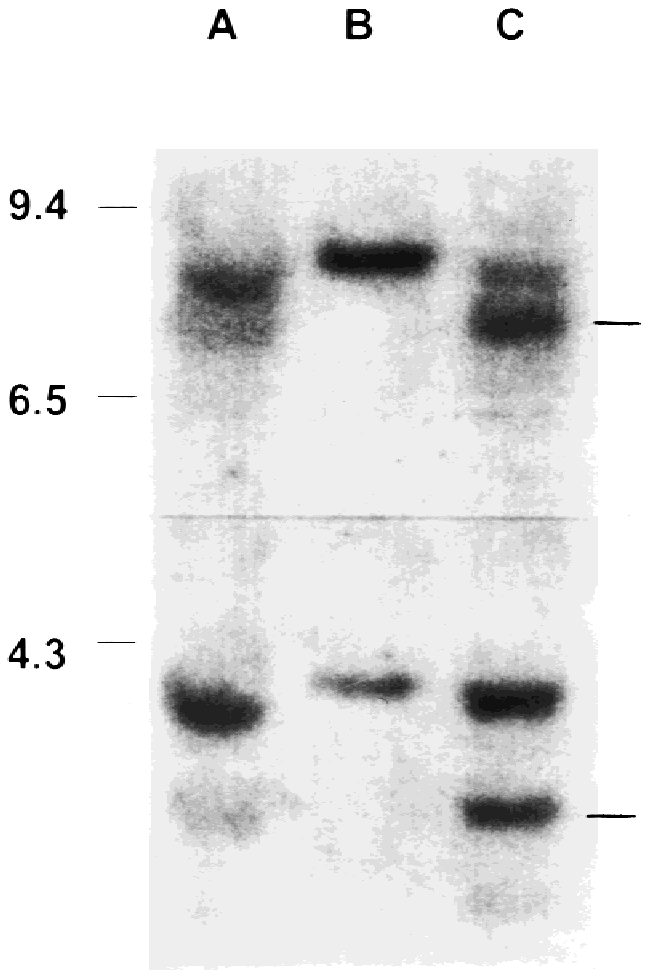

Fig. 3. T-cell receptor rearrangement. Southern blot analysis of the patient's DNA extracted from skin biopsy (A and C) and from peripheral blood lymphocytes (B). DNA was cut with *Eco*RI and probed with β-TCR probe. Gene rearrangement, manifested by two extra bands (see black lines on the right), was found on diagnosis (A) and at the time of hospitalization (C). Peripheral blood lymphocytes showed no gene rearrangement (B). Molecular markers are indicated on the left.

mechanism leading to the eosinophilia, we examined the patient's cytokine profile (Table I). This was consistent with a high TH_2 activity [6]. Her IL-5, -6, and -10 levels were extremely high, whereas her IL-2 and IFN-γ levels (TH_1 profile) were low. The β_2 microglobulin levels were in the normal range, as reported for CTCL [21], whereas soluble IL-2 receptor (sIL-2R) levels were very high. High levels of sIL-2R are associated with an active state of lymphomas including CTCL [21,22]. Treatment with high-dose intravenous Methylprednisolone decreased the IL-5, IL-6, and sIL-2R levels, although, they remained high. We believe that eosinophilic pneumonia as well as the peripheral eosinophilia in this patient is probably secondary to high TH_2 cytokine levels induced by tumor cells.

The cytokine production may originate from the tumor cells or from the reactive inflammatory cells. The homogenous TH_2 cytokine profile in our case and similar previous descriptions [3,4,23] point to the tumor cells as the probable source. The eosinophilic pneumonia appeared during a clinical remission from the cutaneous lymphoma following therapy. Despite clinical remission, the patient had residual disease as shown by T-cell receptor rearrangement (Fig. 3) and the high levels of soluble IL-2 receptors. We presume that the therapy may have caused cytokine release from injured tumor cells and that the bulk of residual malignant T cells produced sufficient IL-5 to cause eosinophilia and pneumonia.

We suggest that eosinophilic pneumonia should be considered as a possible diagnosis in patients with CTCL who have respiratory complaints, especially those who have peripheral eosinophilia. Corticosteroid treatment may be necessary for patients undergoing therapy for CTCL when eosinophilia is present to prevent toxic injury to organs, such as the lungs.

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